Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

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Histoplasmosis (Last updated September 13, 2019; last reviewed September 13, 2019)

Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. The fungal infection is endemic to the central and south-central United States, where it is especially common in the Ohio and Mississippi River valleys. Histoplasmosis is also found in Latin America and the Caribbean and less commonly in other parts of the world. In endemic areas, the annual incidence rate may approach 5% among individuals with HIV. A CD4 T lymphocyte (CD4) count <150 cells/mm^3 is associated with an increased risk of symptomatic illness in people with HIV.[1,2]

Histoplasmosis is acquired by inhalation of microconidia that form in the mycelial phase of the fungus in the environment. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. Diminished cellular immunity can lead to reactivation of a quiescent focal infection acquired years early; this is the presumed mechanism for disease occurrence in nonendemic areas.

Clinical Manifestations

In patients with HIV, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough, chest pain, and dyspnea occur in approximately 50% of patients.[1,3] Central nervous system (CNS), gastrointestinal (GI), and cutaneous manifestations occur in a smaller percentage of patients. Approximately 10% of patients experience shock and multi-organ failure. Patients with CNS histoplasmosis typically experience fever and headache, and if brain involvement is present, seizures, focal neurological deficits, and changes in mental status.[4] GI disease usually manifests as diarrhea, fever, abdominal pain, and weight loss.[5] In a case series of patients with AIDS in Panama, diarrhea was seen in 50% of the patients with histoplasmosis.[6] For patients with CD4 counts >300 cells/mm^3, histoplasmosis is often limited to the respiratory tract and usually presents with cough, pleuritic chest pain, and fever.

Diagnosis

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated and acute pulmonary histoplasmosis[7] but is insensitive for chronic forms of pulmonary infection. In a study using a newer quantitative assay, *Histoplasma* antigen was detected in 100% of urine samples and 92% of serum samples from people with AIDS and disseminated histoplasmosis.[8] Antigen detection in bronchoalveolar lavage fluid may also be useful method for diagnosis of pulmonary histoplasmosis.[9] In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by white blood cells, and histopathological examination of biopsy material from involved tissues often demonstrate the characteristic 2 to 4 μm in diameter budding yeast cells.

H. capsulatum can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions, or from samples from other involved sites in >85% of patients with AIDS and disseminated histoplasmosis, but the organism requires several weeks to grow.[10] Serologic tests are less useful than antigen assays in patients with AIDS and disseminated histoplasmosis but may be helpful in patients with pulmonary disease who have reasonably intact immune responses.[10,11]

The diagnosis of *Histoplasma* meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[4] In a recent review of CNS histoplasmosis that included patients with HIV infection, cultures were positive in 38% of patients.[12] *Histoplasma* antigen can be detected in CSF in a far greater number of cases, and antibodies against *H. capsulatum* are seen in approximately one-half of cases.[12] A positive antigen or antibody test result from CSF is diagnostic for histoplasmosis. In cases in which none of these specific tests is positive, a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not attributable to another cause.

Preventing Exposure

Individuals with HIV who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to *H. capsulatum*, but those with CD4 counts <150 cells/mm^3 should avoid activities associated with an increased risk for histoplasmosis **(BIII)**. These activities include creating dust when working with surface soil; cleaning chicken coops; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves.

Preventing Disease

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis, although not mortality, in patients who have advanced HIV and who live in areas in which histoplasmosis is highly endemic.[13] Some experts would give prophylaxis with itraconazole at a dose of 200 mg daily to patients with CD4 counts <150 cells/mm^3 who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**.

If used, primary prophylaxis can be discontinued in patients on antiretroviral therapy (ART) once CD4 counts are ≥150 cells/mm^3 for 6 months and HIV-1 viral load is undetectable **(BIII)**. Prophylaxis should be restarted if the patient's CD4 count falls to <150 cells/mm^3 **(BIII)**.

Treating Disease

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily); the liposomal formulation induced a more rapid and complete response, lowered mortality rates, and reduced toxicity.[14] Based on these findings, patients with moderately severe to severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for ≥2 weeks or until they clinically improve **(AI)**. Amphotericin B lipid complex (5 mg/kg daily) can be used if cost is a concern or patient cannot tolerate liposomal amphotericin B **(AIII)**.

Step-down therapy to oral itraconazole, 200 mg three times a day for 3 days, and then 200 mg two times a day, should be given for ≥12 months **(AII)**.[15] Because absorption of itraconazole can be erratic and because of potential drug interactions between itraconazole and protease inhibitors, efavirenz, rilpivirine, etravirine, and many other drugs, random serum levels of itraconazole should be measured 2 weeks after the start of therapy. A serum level of 1 to 2 µg/mL is recommended, and the number and severity of adverse events increase when levels are ≥4 µg/mL.[16]

In patients with less severe disseminated histoplasmosis, oral itraconazole, 200 mg three times daily for 3 days followed by 200 mg twice daily, is appropriate initial therapy **(AII)**.[15,17] The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption, but it is less well tolerated than the capsule formulation. The capsule formulation should be given with food and cannot be used when the patient requires gastric acid inhibiting drugs. A new formulation of itraconazole, SUBA-itraconazole, has improved absorption and may prove useful in treating histoplasmosis; however, this agent cannot be recommended, pending further data on its use for this purpose.

The management of acute pulmonary histoplasmosis in a patient with HIV who has a CD4 count >300 cells/mm^3 is the same as for an immunocompetent patient **(AIII)**.[15]

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dosage of 5 mg/kg IV daily for 4 to 6 weeks **(AIII)**. This initial IV therapy should be followed by maintenance therapy with oral itraconazole at a dose of 200 mg two or three times daily for ≥12 months and until resolution of abnormal CSF findings **(AIII)**.[15]

Oral posaconazole and voriconazole have been reported to be effective in treating histoplasmosis in a small number of patients with AIDS or other immunosuppressive conditions[18-21] and may be reasonable alternatives for patients who are only moderately ill and intolerant of itraconazole and for those who have *Histoplasma* meningitis and require long-term antifungal therapy **(BIII)**. If voriconazole is used, trough serum levels should be measured after 5 days of therapy with a goal of achieving a concentration of 2 to 5 ug/mL. Concentrations are highly

variable among different patients and over time, within a given patient. Concentrations can vary because of absorption issues and drug-drug interactions. Neurotoxicity and hepatotoxicity are associated with serum levels >5 ug/mL, but individual patients can experience adverse effects with lower serum levels. Posaconazole serum levels should be measured after 5 days of therapy to ensure adequate absorption, with a goal of achieving a concentration >1 ug/mL.

Fluconazole is less effective than itraconazole for treatment of histoplasmosis, but has been shown to be moderately effective at a dose of fluconazole 800 mg daily. At this dose, fluconazole may be a reasonable alternative for those intolerant of itraconazole and for long-term therapy for *Histoplasma* meningitis **(CII)**.[22] Isavuconazole has been used in too few patients with histoplasmosis to be recommended at this time. The echinocandins do not have activity against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining response to therapy. A rise in antigen level suggests relapse.

Individuals with HIV diagnosed with histoplasmosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) has been uncommonly reportedly in patients with HIV who have histoplasmosis.[23,24] ART should, therefore, not be withheld because of concern for the possible development of IRIS **(AIII)**.

All triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

Managing Treatment Failure

Liposomal amphotericin B should be used in patients who are severely ill or who have failed to respond to initial azole antifungal therapy **(AIII)**. Oral posaconazole and oral voriconazole are reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**;[18-21] fluconazole at a dose of 800 mg daily also can be used **(CII)**.[22] Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or protease inhibitors. Posaconazole has fewer known drug interactions with ART medications than voriconazole.

Prevention of Relapse

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered to patients with severe disseminated infection or CNS infection **(AIII)** and after re-induction therapy to those whose disease relapsed despite initial receipt of appropriate therapy **(BIII)**. Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.[25,26] The role of voriconazole or posaconazole has not been evaluated in sufficiently powered studies.

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that it was safe to discontinue itraconazole treatment for histoplasmosis in patients who had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum or urine antigen <4.1 units, and CD4 counts ≥150 cells/mm^3; and had been on ART for 6 months.[25] No relapses were evident among 32 study participants who were followed for a median of 24 months. Thus, it appears safe to discontinue suppressive azole antifungal therapy in patients who meet the criteria described above, have a serum or urine antigen below the limit of quantification in ng/mL (current terminology that replaces the term "units"), and have an undetectable viral load **(AI)**. Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^3 **(BIII)**.[25]

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis

in pregnant patients. Extensive clinical experience with amphotericin B has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of >300 women with first trimester exposure did not show an increased risk of congenital malformation.[27,28] However, in general, azole antifungals should be avoided during the first trimester of pregnancy **(BIII)**. Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses ≥400 mg/day throughout or beyond the first trimester of pregnancy.[29] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short-term exposure to fluconazole.[30,31] On the basis of the reported birth defects, the Food and Drug Administration has changed the pregnancy category for fluconazole for any use other than a single, low dose for treatment of vaginal candidiasis from category C to category D (see the FDA Drug Safety Communication).

In animals, voriconazole (at doses lower than recommended human doses) and posaconazole are teratogenic and embryotoxic. There are no adequately controlled studies of these drugs in humans. Use of voriconazole and posaconazole **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 1 of 3)

Preventing First Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- CD4 count <150 cells/mm^3 and at high risk because of occupational exposure or residence in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**

Preferred Therapy:

- Itraconazole 200 mg PO once daily **(BI)**

Criteria for Discontinuing Primary Prophylaxis **(BIII)**:

- Patient on ART, *and*
- CD4 count ≥150 cells/mm^3, *and*
- Undetectable HIV-1 viral load for 6 months

Indication for Restarting Primary Prophylaxis:

- CD4 count <150 cells/mm^3 **(BIII)**

Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy

Preferred Therapy:

- Liposomal amphotericin B at 3 mg/kg IV daily **(AI)**

Alternative Therapy:

- Amphotericin B lipid complex at 5 mg/kg IV daily **(AIII)**

Duration:

- For ≥2 weeks or until clinically improved

Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO three times a day for 3 days, then two times a day for ≥12 months **(AII)**, with dosage adjustment based on interactions with ART and itraconazole serum concentration

Treating Less Severe Disseminated Disease

Induction and Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day for ≥12 months **(AII)**, with dose adjustment based on interactions with ART and itraconazole serum concentration

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 2 of 3)

Treating Less Severe Disseminated Disease, continued

Alternative Therapy:

- **Note:** These recommendations are based on limited clinical data for patients who are intolerant to itraconazole and who are only moderately ill.
- Posaconazole, extended release tablet 300 mg PO twice daily for 1 day, then 300 mg PO once daily **(BIII)**
- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily **(BIII)**
- Fluconazole 800 mg PO once daily **(CII)**

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks):

- Liposomal amphotericin B 5 mg/kg IV daily **(AIII)**

Maintenance Therapy

- Itraconazole 200 mg PO two or three times a day for ≥12 months and until resolution of abnormal CSF findings with dosage adjustment based on interactions with ART and itraconazole serum concentration **(AIII)**

Alternative Therapy:

- **Note:** These recommendations are based on limited clinical data for patients intolerant to itraconazole.
- Voriconazole 400 mg PO two times a day for 1 day, then 200 mg PO two times a day **(BIII)**
- Posaconazole 300 mg extended release tablet PO twice daily for 1 day, then 300 mg PO once daily **(BIII)**
- Fluconazole 800 mg PO once daily **(CII)**

Long Term Suppressive Therapy

Indications:

- Severe disseminated or CNS infection after completing ≥12 months of treatment **(AIII)**, *and*
- Relapse despite appropriate initial therapy **(BIII)**

Preferred Therapy:

- Itraconazole 200 mg PO once daily **(AIII)**

Alternative Therapy:

- Posaconazole 300 mg extended release tablet PO once daily **(BIII)**
- Voriconazole 200 mg PO twice daily **(BIII)**
- Fluconazole 400 mg PO once daily **(CII)**

Criteria for Discontinuing Long Term Suppressive Therapy **(AI)**:

- Received azole treatment for >1 year, *and*
- Negative fungal blood cultures, *and*
- Serum or urine *Histoplasma* antigen below the level of quantification, *and*
- Have an undetectable HIV viral load, *and*
- CD4 count >150 cells/mm^3 for ≥6 months in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 count <150 cells/mm^3 **(BII)**

Other Considerations

- Itraconazole serum concentrations should be measured in all patients after 2 weeks of therapy (time it usually takes to reach steady state) to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions **(AIII)**. Random serum concentrations (itraconazole plus hydroxyitraconazole) should be between 1 to 2 µg/mL. Concentrations >4 µg/mL are associated with increased frequency and severity of adverse effects.
- Itraconazole oral solution is preferred over the capsule formulation because of improved absorption but is less well tolerated. However, it is not necessary to use the oral solution if itraconazole concentration is >1.0 µg/mL with the capsule formulation.
- Voriconazole trough serum levels should be measured after 5 days of therapy (time it usually takes to reach steady state) with a goal of achieving a concentration of 2 to 5 ug/mL. Levels are highly variable among patients, and for individual patients, levels can vary because of drug-drug interactions. Neurotoxicity and hepatotoxicity are associated with serum levels >5 ug/mL, but individual patients can experience adverse effects with lower serum levels.
- Trough posaconazole serum levels should be measured after 5 days of therapy (time it usually takes to reach steady state) to ensure adequate absorption, with a goal of achieving a concentration >1 ug/mL.
- Acute pulmonary histoplasmosis in patients with HIV with CD4 count >300 cells/mm^3 should be managed the same as in immunocompetent patients **(AIII)**.
- All triazole antifungals have the potential to interact with certain ART agents and other anti-infective agents. These interactions are complex and can be bidirectional. Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines lists these interactions and recommends dosage adjustments where feasible.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, CSF = cerebrospinal fluid; CYP = cytochrome P450; IV = intravenous; PI = protease inhibitor; PO = orally

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